UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/772,790	01/30/2001	Endre Markovits Schersl	HAR-104	2203

7590 03/08/2006

David I. ROCHE
BAKER & McKENZIE
130 E. Randolph Drive
Chicago, IL 60601

EXAMINER	
COTTON, ABIGAIL MANDA	

ART UNIT	PAPER NUMBER
1617	

DATE MAILED: 03/08/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/772,790	SCHERSL, ENDRE MARKOVITS	
	Examiner	Art Unit	
	Abigail M. Cotton	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 December 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *70-80* is/are pending in the application.

4a) Of the above claim(s) *74-80* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *70-73* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on December 13, 2005, has been entered.

Claims 70-80 are pending in the application, with claims 74-80 being withdrawn as drawn to a non-elected invention. Accordingly, claims 70-73 are being examined on the merits herein.

Applicant's arguments filed December 13, 2005 have been fully considered but they are not persuasive. The Hasegawa reference (of record) is being replaced by the teachings of U.S. Patent No. 5,604,216 to Horrobin, as the complete copy of the Hasegawa reference beyond the abstract is not available.

Election/Restrictions

Newly submitted claims 74-80 are directed to an invention that is independent or distinct from the elected invention. In particular, the claims are directed to a method for

lowering LDL-cholesterol levels or elevating HDL-cholesterol levels in blood of a mammal by orally administering one or more esters of a polycosanol, which corresponds to Group II as described in the Requirement for Restriction/Election mailed on June 16, 2002, which paper also described the reasons for the restriction. However, Applicants elected the invention of Group I, directed to a composition having the one or more esters of the polycosanol, in the response submitted May 13, 2003, and this restriction requirement was made final in the office action mailed June 18, 2003.

Thus, Applicants are entitled to examination of inventions corresponding to compositions of Group I, but not the methods of Group II, in the present application. Accordingly, claims 74-80 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Claim Objections

Claims 71-72 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. In particular, claim 70, from which claims 71-72 depend, recites that the carboxylic acid is selected from the group **consisting of** eicosapentaenoic acid, docosahexaenoic acid, linoleic acid, arachidonic acid and linolenic acid, and thus the carboxylic acid is limited to these five specifically recited acids, and also recites that the polycosanol is selected

from the group **consisting of** docosanol, tetracosanol and hexacosaol, and thus the polycosanol is limited to the three recited alcohols.

In contrast, claim 71 recites that the alcohol can be docosanol, tetracosanol and hexacosanol, as in claim 70, and further recites that the alcohol can comprise alcohols other than those recited in claim 70, such as eicosanol, tricosanol and octacosanol. Thus, claim 71 recites alcohols that are outside the scope of the claim from which it depends, and thus claim 71 fails to further limit claim 70. Similarly, claim 72 recites that the carboxylic acid can contain from 2 to 22 carbon atoms, and thus recites carboxylic acids that are other than those recited in claim 70, and fails to further limit the claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Claim 70 is objected to because "eicosapentaenoic acid" is spelled incorrectly as "eicosapentaeinoic acid," and "linoleic acid" is spelled incorrectly as "linoeic acid." Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 71 is rejected under 35 U.S.C. 112, second paragraph, as having a lack of antecedent basis for the phrase "primary aliphatic alcohol" as recited in the claim. Claim 70, from which claim 71 depends, recites a polycosanol, but does to recite a primary aliphatic alcohol. Accordingly, it is not clear what alcohol is being referred to, and thus the metes and bounds of the claim are not clear. Appropriate correction is required.

Claim 72 is rejected under 35 U.S.C. 112, second paragraph, as having a lack of antecedent basis for the phrase "the acid moiety" as recited in the claim. Claim 70, from which claim 72 depends, recites a carboxylic acid, but does to recite an acid moiety. Accordingly, it is not clear what moiety is being referred to, and thus the metes and bounds of the claim are not clear. Appropriate correction is required.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 70-73 are obvious under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,502,077 to Breivik et al, issued March 26, 1996, U.S. Patent No. 5,604,216 to David F. Horrobin, issued February 18, 1997, U.S. Patent No. 5,663,156 to Granja et al, issued September 2, 1997, and U.S. Patent No. 3,031,376 to Levin et al, issued April 24, 1962, in view of Bundgaard ("Design of Prodrugs" Chapter 1, page 1, of record.)

Breivik et al. teaches a fatty acid composition comprising fatty acids such as eicosapentaenoic acid and docosahexaenoic acid, that can be provided for the treatment of cardiovascular diseases (see abstract, in particular.) The compounds can be provided with a pharmaceutically acceptable carrier, excipient or diluent for treating cardiovascular disease such as hypercholesterolemia, hypertension, and hyperglyceridemia (see abstract, column 1, lines 14-17 and Tables 1-11, in particular.) Beivik et al. teaches that the fatty acid compounds can be provided in the form of free acids or as esters, such as EPA ethyl ester and DHA ethyl ester (see column 3, lines

50-60, column 2, lines 14-22 and the Example at column 11, line 30-38 and claim 12, in particular.)

Horrobin teaches a composition containing esters of fatty acids such as linoleic acid (see abstract, in particular), and teaches that the fatty acids and fatty acid esters are suitable for the treatment of coronary and peripheral arterial disease and have desirable actions of the cardiovascular system (see column 2, lines 37-50, in particular.)

Thus, Beivik et al. and Horrobin teach providing esters of the carboxylic acids recited in claims 70 and 72 for the treatment of cardiovascular disease, and teach that the esters of the carboxylic acids can be substituted for the free acids to provide the beneficial effects.

Granja et al. teaches that primary aliphatic alcohols of 22 to 28 carbon atoms (polycosanols), such as tetracosanol, hexacosanol, heptacosanol, octacosanol, and triacontanol as recited in the claims (see abstract, in particular.) Granja et al. teaches that the alcohols can be provided for the treatment of hypercholesterolemia and atherosclerosis (see abstract, Table 1-2 at column 3, Examples 11-13 at column 12-14 and clams 1-20, in particular.)

Levin et al. discloses a composition comprising one or more esters of tetracosanol, hexacosanol and triacontanol (see column 1, lines 13-20, in particular.)

Levin teaches a general formula for the active compounds that is R-O-X, where R is an alkyl radical having 24, 26, 28 or 30 carbon atoms, and X can be hydrogen or an acid radical, such as an organic acid radical (see column 3, lines 58-72, in particular), and thus teaches that the free alcohol is interchangeable with the ester derivative of the alcohols. Levin et al. teaches that the composition is suitable for stimulating or improving heart response (see column3, lines 50-58, in particular.) Regarding claim 73, Levin et al. teaches that such a therapeutic composition can be provided with food as a carrier such as vegetable oils (see column 4, lines 10-12 and 34-38), and thus teaches the pharamaceutically acceptable component as recited in claim 73.

Accordingly, Granja et al. and Levin et al. teach the polycosanols as recited in claims 70 and 71 are suitable for improving heart response and for the treatment of hypercholesterolemia and atherosclerosis, and Levin et al. teaches that the ester form of the polycosanols is interchangeable with the free acid. Levin et al. further teaches providing such treatment composition with food as a carrier, such as vegetable oil.

Breivik et al, Horrobin, Granja et al, and Levin et al. teach providing ester forms of the recited carboxylic acids and ester forms of the recited alcohols for the stimulation of the heart and treatment of cardiovascular diseases and conditions. The references do not specifically teach that the ester forms are the ester of the recited carboxylic acid with the recited alcohol.

Bundgaard teaches that esters of actives are some of the most common prodrugs since esters of actives containing hydroxyl and carboxyl groups (i.e. hydroxyl groups of an alcohol and carboxyl groups in a carboxylic acid) are hydrolyzed within the body (in vivo) by cleaving the ester bond to regenerate the active drug substances (se the bottom paragraph at page 1, in particular.)

Accordingly, one of ordinary skill in the art at the time the invention was made would have found it obvious to provide esters of the carboxylic acid and polycosanol, as taught by Breivik et al, Horrobin, Granja et al, and Levin et al, in the form of a combined ester of the carboxylic acid and polycosanol that serves as a prodrug that is cleaved in vivo, as taught by Bundgaard, to form the separate carboxylic acid and polycosanol components, because Breivik et al, Horrobin, Granja et al, and Levin et al. all teach that the separate carboxylic acids and polycosanols as well as their esters are suitable for the stimulation of the heart and treatment of cardiovascular diseases, and Bundgaard elucidates the means by which such esters provide therapeutic effect, namely by cleaving of the ester bond to provide the desired separated compound. Thus, one of ordinary skill in the art at the time the invention was made would have been motivated to form an ester prodrug having the carboxylic acid and polycosanol moieties, with the expectation of providing a suitable means for delivery of the individual therapeutic agents for the treatment of cardiovascular disease and the treatment of the heart.

Response to Arguments

Applicant's arguments filed December 13, 2005 have been fully considered but they are not persuasive.

In particular, Applicant's argue that olestra is an example of an ester of a fatty acid that is not hydrolysable in vivo (see page 6, first full paragraph), and thus argue that it is not prima facie obvious that pancreatic esterases would act on polycosanol esters with PUFA to hydrolyze the compound in vivo.

The Examiner notes that the references as cited suggest providing ester forms of the carboxylic acids and polycosanols as recited, and would motivate one of ordinary skill in the art to combine the compounds in ester form to provide a prodrug of the two compounds. The Examiner acknowledges Applicants assertion that Olestra, which is a sucrose polyester, is an ester that does act in accordance with these teachings.

Nonetheless, the expectation that an ester such as Olestra would indeed hydrolyze in vivo, and the surprise that it does not is demonstrated in Applicants own arguments and admissions in the response filed March 24, 2005. Applicant's argue that:

"there are other esters which are not cleaved by neither of the above mechanisms, Bundgaard notwithstanding. Surely, the skilled artisan should have been

aware, at the time our invention was made, of the well known case of Olestra and the story of its development. Olestra is the generic name for sucrose esters of fatty acids. It was developed by Procter and Gamble (trade name Olean.) Its intend use was as an ingredient in a substitute of mother milk under the assumption that the compounds once hydrolyzed within the body would generate sucrose and fatty acids, essential nutrients for infants. To the surprise of the researchers, Olestra, as it turned out, was neither digested nor absorbed; that is, it was not cleaved by pancreatic lipases, and passed through the body unchanged .."

Thus, by Applicant's own admission, esters of fatty acids such as Olestra were expected by those of ordinary skill in the art to undergo hydrolysis in vivo. Instead, Olestra proved to be an exception to the generally accepted mechanism of the action of pancreatic lipases on fatty acid esters. Thus, with the exception of outliers such as Olestra, one of ordinary skill in the art at the time the invention was made would have a reasonable expectation, as did those testing Olestra, that the fatty acid esters would hydrolyze in vivo, as is also taught by Buundgard.

Applicants further argue that the Examiner is using her own knowledge to predict which esters are or are not cleavable. The Examiner refers Applicants to the teachings of the references as discussed above, which teach the suitability and interchangeability of fatty acid and alcohol esters with the free acids and esters, and the teachings of Bundgaard which generally disclose the hydrolyzation of the ester bond in vivo.

Applicants furthermore request that the Examiner provide an affidavit under 37 CFR 104(d)(2), and request that the affidavit to state something which Applicants appear to have accidentally omitted, as the line after the request merely states "Insert B." 37 CFR 104(d)(2) relates to affidavits made when an argument of obviousness is being based on the Examiner's own knowledge. The Examiner refutes the assertion that the obviousness rejection is being based on her own knowledge, as the rejection is being based on the teachings of the references as discussed above. Accordingly, an affidavit under 37 CFR 104(d)(2) is not considered to be relevant to the matters at issue in the case.

Applicants furthermore argue that U.S. Patent No. 5,932,562 to Ostlund, Jr. discloses beta-sitostanol esters of fatty acids that exhibit higher cholesterol lowering effects that the beta-sitostanol alone. As Applicants have not pointed out the section of the Ostlund, Jr. reference that is being used to shown the improved performance of the esters, the Examiner is not sure which results of Ostlund, Jr. are being used to formulate Applicant's arguments. However, the Examiner notes that Ostlund, Jr. teaches that phytosterol is combined with phospholipids to form an aqueous vesicular complex that can enter the intestinal micelle phase (see column 4, liens 6-25, in particular), and the teaches that the sterol and phospholipid are mixed to provide a micellar mix with vesicles (see column 4, liens 54-62, in particular.) Thus, Ostlund, Jr teaches forming vesicles having the sterol with improved cholesterol absorption

lowering effects, but Ostlund, Jr. does not appear to teach administration of an ester with fatty acids of the compounds.

Accordingly, the claims are obvious over the references for the reasons as discussed above.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Abigail M. Cotton whose telephone number is (571) 272-8779. The examiner can normally be reached on 9:30-6:00, M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

AMC

CHEEN FADIMANCHUI
SUPERVISORY PATENT EXAMINER